Examiner. It is respectfully submitted that, in view of the discussion presented below and of the Declarations included herewith, the outstanding rejections have been overcome and the application is in condition for allowance.

Claims 1-96 are pending. Claims 11-16 and 19-34 were previously withdrawn due to an election-of-species requirement.

Claim 1 has been amended to reflect only the ionizable cellulosic polymers set forth in claim 52. Because the ionizable polymers are all cellulosic, the dependency of claim 50 has been changed to omit dependency from claim 1.

Claim 56 has been amended to omit its dependence from claim 2.

It is noted that claim 1 (and dependent claims to the extent they depend therefrom) is now allowable. Claim 52 (now incorporated into claim 1) was rejected over Appel but not over Sikorski. As Applicants discuss below, Appel has been removed as a reference by virtue of the Rule 131 Declaration submitted herewith. Thus claim 1 is free of the rejection over both Appel and Sikorski. The term "cellulosic" does not appear in amended claim 1, thus claim 1 is free of the Section 112 rejection raised by the Examiner in respect of claims 49-55. No further issues remain outstanding in respect of claim 1. Allowance of claim 1 and claims dependent therefrom is respectfully requested.

Claim 2 has been amended to state that the composition provides a maximum concentration of a CETP inhibitor in a use environment that is at least about ten-fold the maximum concentration provided by a control composition comprising an equivalent amount of the CETP inhibitor and free from the (concentration-enhancing) polymer. Support is in the application at page 7, lines 13-19.

Claim 2 has also been amended, to provide antecedent basis, by introducing "CETP" as an acronym.

Claims 49-55 continue to be rejected under 35 USC §112, second paragraph. The Examiner continues to maintain that the claims are indefinite due to the term "cellulosic".

The rejection is traversed on the bases previously offered by Applicants, namely that the term "cellulosic" is well understood in the art and that Applicants have fully disclosed and extensively exemplified the term in their specification. Applicants' arguments from their previous response (January 12, 2004) are incorporated herein by reference in this respect. In further support of their arguments, Applicants enclose, as Attachment 1, pages 169-175 from "Controlled Release Of Biologically Active Agents", by Richard W. Baker, Copyright 1987, published by John Wiley & Sons. Pages 169-175

constitute a Section entitled "Cellulosic Polymers", this alone demonstrating that the term is well known and understood in the art. The section additionally demonstrates, in context, that one skilled in the art uses "cellulosic" to have the same meaning intended by Applicants - - a polymer having a cellulose backbone in which at least some of the hydroxyl groups of the glucose repeat units have been reacted or derivatized to modify the cellulose structure.

The Examiner is again urged to reconsider and withdraw the rejection.

Claims 1-10, 17, 18, and 35-96 were rejected under 35 U.S.C. 102(e) as being anticipated by Appel, US 6,706,283. Although Applicants do not necessarily agree with the rejection, submitted herewith is the Declaration under Rule 131 of Douglas A. Lorenz, an inventor in the instant application, that removes Appel as a reference. The Lorenz declaration demonstrates, through the inclusion of copies of laboratory notebook pages from which the dates have been redacted, that the invention was made in the United States at least by the date of February 9, 1999, a date earlier than the effective date of Appel. As a consequence, Appel has been removed as a reference against Applicants and it is respectfully requested that the rejection under 35 U.S.C. 102(e) be withdrawn.

Claims 1-10, 17, 18, 35-51, 56-86 and 88 continue to be rejected under 35 U.S.C. 102(b) as being anticipated by Sikorski, WO 99/14204. The Examiner commented as follows:

> 4. Claims 1-10, 17, 18, 35-51, 56-86 and 88 remain rejected under 35 U.S.C. 102(b) as being anticipated by Sikorski (WO 99/14204).
>
> 5. Applicants' arguments filed 01/12/04 have been fully considered but they are not persuasive.
>
> Specifically applicants argue that Sikorski does not disclose a solid amorphous dispersion.
>
> It is respectfully noted that the instant invention in generic claim 1 is a composition that comprises a solid amorphous dispersion and concentration-enhancing polymer selected from the group consisting of hydroxypropyl methyl cellulose, etc. Sikorski starts from a powder form of CETP and powder is amorphous except powder is shown not to be amorphous to the contrary. Secondly, spray drying, a process of tablet formation results in formation of dispersion. Therefore, the rejection over Sikorski is maintained. [Office Action, page 3]

As a preliminary comment, it is noted that the Examiner appears to have focused on the following statement in Sikorski:

> Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. [WO 99/14204, page 84, lines 27-29].

As a further preliminary comment, Applicants note that the Examiner's reference in the Office Action to "spray drying" (see the above quotation from the Office Action) is not understood. Applicants conducted two full text searches of Sikorski and determined that neither the word "spray" nor the word "drying" appears in WO 99/14204, meaning that the phrase "spray drying" does not appear either. It is unclear to Applicants why the Examiner mentioned "spray drying" in connection with a reference that does not disclose it. It is noted that the entire text of the sentence from the Office Action that mentioned spray drying is

> Secondly, spray drying, a process of tablet formation results in formation of dispersion. [Page 3 of the Office Action, next-to-last line].

In context, the Examiner may have been attempting to establish a link between Sikorski's mere mention of tablets and Applicants' disclosure of spray drying as a preferred process for making dispersions. If that is in fact the case, then the statement is traversed. Spray drying is not a process used specifically for making tablets. Spray drying is defined, quite simply, as follows:

> Atomization of a solution of one or more solids via a nozzle, spinning disk, or other device, followed by evaporation of the solvent from the droplets is termed spray-drying.

See Chapter 37, page 681 of "Remington: The Science and Practice of Pharmacy", 20th Edition, Edited by Alfonso R. Gennaro, Published by Lippincott Williams & Wilkins, which contains the definition just quoted. A copy of the relevant pages from Remington is appended hereto as Attachment 2, the relevant text having been highlighted for convenience. Spray drying is a process that may be used to treat an active or an excipient that is, in turn, used to make a dosage form. But, it is not, *per se*, a tableting or

tablet-making process. There is nothing in Sikorski that would otherwise connect his mere mention of tablets with spray dried dispersions of the type disclosed in Applicants' specification.

The Office Action also stated that

> Sikorski starts from a powder form of CETP and powder is amorphous except powder is shown not to be amorphous to the contrary. [Page 3, second and third lines from bottom]

The statement is either traversed and/or its significance is not understood. The examiner was presumably referring to Sikorski's statement at page 84, lines 32-33 where Sikorski states, "...These solutions and suspensions may be prepared from sterile powders or granules..." It is not understood how or why the Examiner concluded that a drug is necessarily amorphous from the fact that it can be in powder form. The two concepts, "powder" and "amorphous," are in no way causally connected or related. One does not follow from the other. Attachment 2 (Remington, discussed above) in fact makes the following statement on page 681 (relevant text is highlighted) in respect of the powders produced by spray drying:

> The particles produced are aggregates of primary particles consisting of crystals and/or amorphous solids, depending on the rate and conditions of solvent removal.

Thus, as Remington confirms, a powdered drug can be either crystalline or amorphous (i.e., in a non-crystalline state, as defined by Applicants at page 9, lines 11-13 of their specification). If the Examiner continues to maintain her reasoning in support of the rejection, it is requested she explain exactly why the fact that a drug is powdered necessarily means that the drug must also be amorphous.

The rejection over Sikorski is additionally respectfully traversed on the basis that (1) the word "dispersion" as used by Sikorski has a clearly different meaning than that for the "solid amorphous dispersion" required by Applicants and (2) at least one other element also required by Applicants is missing, namely that the dispersion must be amorphous. The fact that these elements are required by Applicants' claims but are undisclosed in Sikorski means that Sikorski cannot be an anticipating reference within the meaning of 35 USC §102(b). It is well settled that if a reference does not disclose all

of the elements and/or limitations of an applicant's claims, that reference cannot be anticipatory. Gechter v. Davidson, 43 USPQ2d 1030 (Fed. Cir. 1997).

Sikorski Does Not Disclose Solid Amorphous Dispersions As Required By Applicants

As a preliminary comment, Applicants note that each of claims 2-4 requires Applicants' composition to comprise a solid amorphous dispersion of a CETP inhibitor and a concentration-enhancing polymer (claim 1 also contains that limitation, but is believed to be allowable, as discussed above, in any event). The Rule 132 Declaration of Dr. William J. Curatolo, one of the inventors in this application, is included with this response in support of Applicants' contention that Sikorski does not disclose a solid amorphous dispersion. Dr. Curatolo testifies that, because Sikorski refers specifically to controlled release formulations, one skilled in the art would immediately realize that Sikorski was referring to a dosage form such as a controlled release matrix tablet, i.e., a tablet of the type in which hydroxypropylmethyl cellulose is included as a matrix material that contains a CETP inhibitor and that releases it in a controlled manner. HPMC formulations, commonly referred to in the art as "HPMC matrix tablets", are used across a wide spectrum of drugs to make controlled release dosage forms. Controlled release formulations in general function by slowing the release of the active pharmaceutical ingredient contained therein. Such formulations generally lower the maximum concentration of dissolved drug relative to pure drug itself. That is exactly the opposite of what Applicants' sought to achieve and the opposite of what Applicants' claims require. Controlled release formulations generally do not increase the maximum concentration of an active pharmaceutical ingredient relative to the active ingredient alone, much less increase the maximum concentration of drug by a factor of at least about 10, as required by claims 2 and 3. Nor does a controlled release formulation of a CETP inhibitor generally act to increase bioavailabilty by a factor of at least 4, as required by claim 4. For these reasons, one skilled in the art could not reasonably view the bare statement quoted from Sikorski as referring to a solid amorphous dispersion like Applicants'. To repeat, controlled release dosage forms (drug plus polymer as disclosed in Sikorski) do not generally increase the maximum concentration and/or bioavailability of a drug. There is no disclosure otherwise in Sikorski that relates to enhancing the maximum concentration of a poorly soluble drug or to increasing its bioavailability.

As Dr. Curatolo also testifies (see paragraph 8) a physical mixture of a drug and a polymer is different from a dispersion of the drug and polymer such as a solid

amorphous dispersion produced by spray drying. Each individual component in a physical mixture retains the individual bulk physical properties, such as melting point, for that component. A solid amorphous dispersion of drug and a dispersion polymer has different physical properties from the individual bulk components, such as a glass transition temperature (Tg, assuming amorphous components) that is usually intermediate between the Tg for the individual components.

For completeness, it is noted that Applicants disclose that their own compositions can be fabricated as controlled release dosage forms. See Applicants' specification starting at page 111, line 12. That disclosure is of dosage forms different from anything disclosed or even remotely suggested in Sikorski, however. A matrix device according to Applicants' invention comprises a solid amorphous dispersion incorporated into a controlled release matrix, which is an erodible, water-swellable, or aqueous-soluble polymer, as explained at page 11, lines 12-37. Such a device therefore comprises a solid amorphous CETP inhibitor/concentration-enhancing polymer dispersion, which is then incorporated into, as the matrix, a second polymer. This disclosure by Applicants is completely different from and unrelated to the disclosure of controlled release by Sikorski. Sikorski, though he mentions the combination of a CETP inhibitor and a polymer in passing, never discloses, suggests, or even hints at controlled release systems containing a solid amorphous dispersion.

To underscore just how completely different the solid amorphous dispersions required by Applicants are from controlled release compositions such as those alluded to in Sikorski, Applicants submit the Rule 132 declaration of Dwayne T. Friesen herewith. The Friesen Declaration demonstrates that, based on concentration enhancement, drug/HPMC mixtures are different and distinct from solid amorphous drug/HPMC dispersions.

Using Drug 2 from the application, paragraph 7 of the declaration compares the concentration enhancement provided by a solid amorphous HPMC/Drug 2 dispersion against the enhancement provided when HPMC is physically mixed with Drug 2 or when Drug 2 is tested alone. The results are disclosed in Exhibit 1. More specifically, paragraph 7 and Exhibit 1 discuss and demonstrate a significantly enhanced concentration of (1) Drug 2 when formulated as a solid amorphous dispersion with HPMC, as compared with little or no concentration improvement achieved by the following control compositions (A) a physical mixture of crystalline Drug 2 with HPMC (B) a physical mixture of amorphous Drug 2 with HPMC and (C) crystalline Drug 2 alone.

The data clearly demonstrate significantly improved concentrations achievable with Applicants' dispersions as compared with little or no improvement for the controls. The data thus demonstrate that physical mixtures and solid amorphous dispersions, despite the fact they may contain the same materials in the same proportions, are different compositions.

Paragraph 8 of the Friesen Declaration and Exhibit 2 similarly demonstrate that compressing a physical mixture of HPMC and Drug 2 into a tablet (as in Sikorski), whether Drug 2 is crystalline or amorphous, offers substantially inferior performance relative to Applicants' solid amorphous dispersions. Again, the data support that solid amorphous dispersions and physical mixtures are distinct compositions.

In summary, taken together, the Curatolo and Friesen Declarations unequivocally demonstrate that (1) Sikorski's allusion to a "dispersion", in context with his reference to a "controlled-release formulation", does not suggest a solid amorphous concentration-enhancing dispersion like Applicants, but rather a physical mixture of drug and HPMC powders; and (2) a composition that is a physical mixture of drug and polymer is a wholly different composition from a solid amorphous dispersion of drug and polymer. Importantly, the declarations demonstrate that Sikorski does not anticipate Applicants.

Sikorski Does Not Disclose Other Elements Of Applicants' Claims

An affirmative element in each of Applicants' claims is the requirement for a pharmaceutical composition comprising a solid amorphous dispersion. In addition to not disclosing a solid amorphous dispersion, Sikorski further fails to disclose a composition in which the drug is **amorphous** (i.e., the drug is in a non-crystalline state). Sikorski never used the word "amorphous" in his application. Sikorski never disclosed an actual formulation of any type comprising one of his compounds. Since Sikorski never disclosed an actual formulation, it is indisputable that he failed to disclose a solid **amorphous** dispersion. Because the element of **amorphous**, is missing from Sikorski, Sikorski does not anticipate Applicants.

For completeness, Applicants note that independent claims 3 and 4 have not been currently amended. The same comments made above in respect of Applicants requiring their composition to comprise a solid amorphous dispersion apply with equal force to claims 3 and 4, however. Both of these claims require a solid amorphous dispersion as an element thereof. Sikorski does not disclose any actual formulation, much less a solid **amorphous** dispersion, hence cannot anticipate.

Applicants additionally note that claims 5-7 depend from claims 1-4 and further specify that a major portion of the cholesteryl ester protein inhibitor is amorphous (claim 5), that the cholesteryl ester protein inhibitor is substantially amorphous (claim 6), and that the cholesteryl ester protein inhibitor is almost completely amorphous (claim 7). These terms are fully defined in Aplicants' specification as meaning, respectively, that at least 60% of the CETP inhibitor in the composition is in amorphous form (page 9, lines 14-16), that the amount of the CETP inhibitor in crystalline form does not exceed about 25% (page 9, lines 18-20), and that the amount of the CETP inhibitor in crystalline form does not exceed about 10% (page 9, lines 22-24). These features represent additional elements that Sikorski never discloses or even touches on.

Claims 8-10, 17, 18, 35-51, 56-86, and 88 all depend, directly or indirectly, and all incorporate the limitations of, one or more of claims 1-4. All of the dependent claims incorporate the elements of (1) a particular group of ionizable cellulosic polymers, (2) a solid amorphous dispersion that effects at least a ten-fold concentration enhancement or (3) at least a four-fold relative bioavailability, i.e., the elements discussed above that are missing from Sikorski. Thus these claims are free of anticipation as well.

In view of the foregoing comments and amendments and the Declarations submitted herewith, it is respectfully submitted that this case is in condition for allowance. A Notice of Allowance is courteously solicited.

Respectfully submitted,

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